**JOINT ASSOCIATIONS OF PERIPHERAL ARTERY DISEASE AND OBJECTIVELY MEASURED PHYSICAL ACTIVITY WITH MORTALITY:
THE HISPANIC COMMUNITY HEALTH STUDY / STUDY OF LATINOS (SOL)**

by
Yumin Gao

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Abstract

Background Peripheral artery disease (PAD) and lower physical activity have been related to each other and increase mortality individually. Yet, their joint prognostic impact has not been systematically examined, especially in Hispanics and with objective measurements on physical activity.

Methods We studied 7,330 Hispanic adults aged 45-74 years at baseline (2008-2011) who adhered to physical activity assessment with accelerometry, Actical. To assess total physical activity level, we divided daily accelerometry counts by wear time and calculated the average across adherent days. For intensity, we used average daily physical activity time spent in sedentary, light, and moderate or vigorous levels. Sedentary time was standardized according to wear time. We quantified independent and joint associations of ankle-brachial index (ABI) categories (≤0.9 [PAD], 0.9-1.4 [reference], and ≥1.4 [possible PAD with uncompressible arteries]) and tertiles of physical activity measures (i.e., sedentary time, light activity, moderate/vigorous activity, and total physical activity level) with mortality using multivariable Cox models accounting for sampling weights.

Results ABI values and each physical activity variable were weakly correlated ($|r|<0.06$). During a median follow-up of 7.1 years, 314 participants died. PAD and all physical activity measures were independently associated with increased risk of mortality. When cross-categories of ABI and physical activity were assessed, they demonstrated joint associations (e.g., hazard ratio 5.87 [95%CI 3.53-9.77] in abnormal ABI [≤0.9 or >1.4] plus the lowest tertile of light physical activity; hazard ratio ~2 in the category of either abnormal ABI or the lowest light physical activity vs. normal ABI plus higher light physical activity), with no significant interactions. Largely similar results were seen in subgroups by age, gender, and Hispanic origins.

Conclusions Abnormal ABI and lower objectively-measured physical activity were independently and jointly associated with mortality risk. Our results suggest the importance of simultaneously evaluating leg vascular condition and physical activity levels in Hispanics.

Primary Reader and Advisor: Dr. Kuni Matsushita

Secondary Reader: Dr. Jennifer Schrack

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Table 1. Baseline Characteristics of Participants by ABI Categories or Tertiles of Sedentary Time, Weighted for Sampling

	Ankle-Brachial Index			Sedentary Time		
Characteristic	**ABI≤0.9**	**0.9<ABI≤1.4**	**ABI>1.4**	**Tertile 1 (Most Active)**	**Tertile 2**	**Tertile 3 (Least Active)**
Total participants, No. (unweighted)	345	6823	162	2444	2443	2443
Age, y	61.0 (0.65)	56.3 (0.17)	61.5 (0.98)	53.7 (0.23)	56.3 (0.26)	59.6 (0.26)
Male, %	34.4 (3.3)	45.1 (0.8)	70.8 (5.4)	52.0 (1.5)	40.8 (1.4)	43.5 (1.3)
Hispanic/Latino background, %						
Mexican	20.1 (3.6)	33.6 (1.8)	29.6 (5.4)	40.6 (2.1)	35.7 (2.2)	23.3 (1.9)
Puerto-Rican	17.2 (2.5)	18.0 (1.1)	20.6 (3.7)	15.3 (1.6)	17.2 (1.4)	21.2 (1.4)
Cuban	43.4 (4.1)	24.8 (2.1)	31.8 (5.7)	23.2 (2.2)	26.6 (2.4)	27.9 (2.3)
Others/mixed	19.3 (2.4)	23.6 (1.2)	17.9 (3.5)	21.0 (1.4)	20.6 (1.3)	27.7 (1.6)
Education status, %						
Less than high school	47.7 (3.7)	39.5 (1.0)	39.3 (5.6)	38.9 (1.7)	38.0 (1.6)	42.8 (1.6)
High school or equivalent	17.5 (3.3)	20.8 (0.7)	21.8 (4.4)	22.1 (1.1)	20.1 (1.2)	19.9 (1.1)
Greater than high school	34.8 (3.4)	39.7 (1.0)	38.8 (5.6)	39.1 (1.7)	42.0 (1.6)	37.3 (1.6)
Acculturation score[a]	1.7 (0.10)	1.8 (0.04)	1.8 (0.13)	1.8 (0.06)	1.8 (0.06)	1.8 (0.05)
BMI (kg/m^2)						
BMI<25	25.5 (3.6)	16.8 (0.7)	17.0 (3.8)	20.1 (1.3)	17.4 (1.1)	14.6 (0.9)
25≤BMI<30	33.8 (3.2)	41.6 (0.9)	25.5 (4.9)	42.4 (1.5)	41.4 (1.3)	38.6 (1.6)
BMI≥30	40.7 (3.2)	41.6 (0.9)	57.5 (5.2)	37.5 (1.6)	41.2 (1.3)	46.8 (1.5)
Smoking status, %						
Never smoker	41.2 (3.7)	55.6 (1.0)	64.5 (5.4)	53.0 (1.7)	53.9 (1.6)	58.1 (1.5)
Former smoker	25.7 (3.0)	25.7 (0.9)	29.3 (5.4)	24.8 (1.5)	27.1 (1.6)	25.5 (1.3)
Current smoker	33.2 (3.6)	18.7 (0.8)	6.2 (1.8)	22.2 (1.4)	19.1 (1.2)	16.4 (1.1)
Diabetes, %	44.2 (3.7)	26.8 (0.9)	46.8 (5.7)	22.7 (1.4)	24.1 (1.3)	37.0 (1.4)
Systolic blood pressure, mmHg	137.3 (1.43)	128.3 (0.34)	136.1 (2.10)	127.3 (0.49)	128.5 (0.55)	131.0 (0.58)
Use of anti-hypertensive medications, %	41.5 (3.6)	25.4 (0.8)	47.1 (5.9)	19.9 (1.2)	24.5 (1.3)	35.1 (1.5)
Total cholesterol, mg/dL	214.4 (3.26)	208.8 (0.85)	201.2 (4.85)	208.6 (1.34)	211.0 (1.62)	207.1 (1.14)
HDL-cholesterol, mg/dL	49.6 (0.93)	49.8 (0.24)	49.0 (1.21)	50.2 (0.51)	50.2 (0.39)	48.9 (0.36)
ABI	0.85 [0.79-0.88]	1.07 [1.01-1.13]	1.66 [1.46-2.00]	1.07 [1.01-1.13]	1.06 [1.00-1.12]	1.06 [0.99-1.12]
Accelerometer wear time, hours/d	15.7 (0.26)	15.8 (0.08)	16.4 (0.41)	15.9 (0.10)	15.4 (0.09)	16.2 (0.12)
Sedentary time, hours/d	12.2 [10.2-14.9]	11.7 [9.8-14.3]	13.4 [10.8-15.4]	9.7 [8.3-12.1]	11.4 [10.0-13.8]	14.2 [11.9-16.1]
Light physical activity time, hours/d	2.9 [2.0-4.3]	3.5 [2.6-4.7]	2.9 [2.1-4.2]	5.1 [4.5-6.0]	3.4 [3.0-3.9]	2.3 [1.8-2.7]
Moderate or vigorous physical activity time, mins/d	6.0 [1.4-15.3]	12.3 [4.5-26.7]	8.4 [1.8-25.7]	23.0 [11.0-42.5]	11.8 [5.0-23.5]	5.2 [1.5-12.8]
Total physical activity level, counts/min/d	108.4 (5.65)	155.9 (2.53)	132.2 (10.60)	256.7 (5.84)	137.7 (2.00)	76.2 (1.41)

Values for continuous variables are given as mean (SE) or median [IQI]; values for categorical variables are given as percentage (SE). Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HDL, high-density lipoprotein; IQI, interquartile interval; SE, standard error.

[a]The acculturation score was derived from the self-reported language spoken at home, nativity, and years of residence in the US, ranging from 0 to 5, with 5 being the highest acculturation level.

Table 2. Adjusted Hazard Ratios (95% CI) of Mortality by ABI Categories or Physical Activity Variables

Exposures	ABI Categories or Tertiles of Physical Activity Variables		
ABI Categories	**ABI≤0.9 (PAD)**	**0.9<ABI≤1.4**	**ABI>1.4**
No. of deaths/N (unweighted)	39/345	250/6823	25/162
Adjusted Hazard Ratios (95% CI)[a,b]	2.36 (1.46-3.81)	1.00 (Reference)	3.39 (1.84-6.25)
Physical Activity Variables[c]	**1st Tertile**	**2nd Tertile**	**3rd Tertile**
Sedentary Time[d]			
Range, hours/d	-5.4 – 11.6	11.6 – 12.9	12.9 – 17.0
No. of deaths/N	52/2444	90/2443	172/2443
Adjusted Hazard Ratios (95% CI)[a]	1.00 (Reference)	1.32 (0.81-2.17)	2.50 (1.54-4.07)
Light Physical Activity Time			
Range, hours/d	0.19 – 2.9	2.9 – 4.2	4.2 – 22.1
No. of deaths/N	172/2444	87/2443	55/2443
Adjusted Hazard Ratios (95% CI)[a]	2.67 (1.66-4.29)	1.22 (0.72-2.07)	1.00 (Reference)
Moderate/Vigorous Physical Activity Time			
Range, mins/d	0 – 6.3	6.4 – 20	20 – 643.5
No. of deaths/N	138/2447	82/2454	94/2429
Adjusted Hazard Ratios (95% CI)[a]	1.57 (1.03-2.41)	0.86 (0.55-1.36)	1.00 (Reference)
Total Physical Activity Level			
Range, counts/min/d	6.8 – 97.0	97.1 – 162.7	162.8 – 3273.9
No. of deaths/N	154/2444	82/2443	78/2443
Adjusted Hazard Ratios (95% CI)[a]	2.07 (1.30-3.29)	1.37 (0.86-2.19)	1.00 (Reference)

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; PAD, peripheral artery disease.
[a] Covariates included age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use.
[b] Hazard ratios of ABI were further adjusted for standardized sedentary time and total physical activity level.
[c] Hazard ratios of each physical activity variable were further adjusted for wear time (except sedentary time).
[d] Sedentary time standardized by wear time.

Table 3. Adjusted Hazard Ratios (95% CI) of Mortality by Cross-Categories of ABI and Physical Activity

ABI Categories	Physical Activity Variables		
	Sedentary Time		**Overall[a]**
	1st and 2nd Tertiles	*3rd Tertile*	
0.9<ABI≤1.4	1.00 (Reference)	1.78 (1.20-2.63)	1.00 (Reference)
ABI≤0.9 (PAD) or ABI>1.4	2.11 (1.09-4.06)	5.40 (3.31-8.79)	2.72 (1.85-4.00)
Overall[a]	1.00 (Reference)	2.11 (1.49-2.98)	P-for-interaction = 0.74
	Light Physical Activity Time[b]		**Overall[a,b]**
	1st Tertile	*2nd and 3rd Tertiles*	
0.9<ABI≤1.4	2.03 (1.40-2.95)	1.00 (Reference)	1.00 (Reference)
ABI≤0.9 (PAD) or ABI>1.4	5.87 (3.53-9.77)	2.13 (1.11-4.09)	2.68 (1.81-3.98)
Overall[a,b]	2.38 (1.71-3.31)	1.00 (Reference)	P-for-interaction = 0.29
	Moderate/Vigorous Physical Activity Time[b]		**Overall[a,b]**
	1st Tertile	*2nd and 3rd Tertiles*	
0.9<ABI≤1.4	1.34 (0.89-2.03)	1.00 (Reference)	1.00 (Reference)
ABI≤0.9 (PAD) or ABI>1.4	4.59 (2.74-7.69)	1.82 (0.99-3.36)	2.91 (1.96-4.32)
Overall[a,b]	1.70 (1.20-2.43)	1.00 (Reference)	P-for-interaction = 0.14
	Total Physical Activity Level[b]		**Overall[a,b]**
	1st Tertile	*2nd and 3rd Tertiles*	
0.9<ABI≤1.4	1.35 (0.90-2.03)	1.00 (Reference)	1.00 (Reference)
ABI≤0.9 (PAD) or ABI>1.4	4.68 (2.81-7.78)	1.70 (0.86-3.36)	2.85 (1.92-4.22)
Overall[a,b]	1.72 (1.22-2.43)	1.00 (Reference)	P-for-interaction = 0.41

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; PAD, peripheral artery disease.
Covariates included age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use and moderate or vigorous physical activity time.

[a] ABI values and each physical activity variable were mutually adjusted.
[b] Hazard ratios were further adjusted for wear time.

Web Table 1. Baseline Characteristics by Tertiles of Light Physical Activity, Weighted for Sampling

	Light Physical Activity Time		
Characteristic	**Tertile 1 (Least Active)**	**Tertile 2**	**Tertile 3 (Most Active)**
Total participants, No. (unweighted)	2444	2443	2443
Age, y	59.5 (0.27)	56.1 (0.27)	53.8 (0.22)
Male, %	43.7 (1.4)	40.4 (1.5)	52.1 (1.4)
Hispanic/Latino background, %			
Mexican	27.5 (2.0)	32.5 (2.2)	39.4 (2.1)
Puerto-Rican	17.9 (1.4)	18.9 (1.3)	17.2 (1.6)
Cuban	31.2 (2.4)	24.7 (2.3)	21.0 (2.1)
Others/mixed	23.4 (1.4)	23.9 (1.5)	22.3 (1.4)
Education status, %			
Less than high school	41.7 (1.6)	37.8 (1.5)	40.2 (1.7)
High school or equivalent	19.6 (1.1)	20.5 (1.2)	22.1 (1.2)
Greater than high school	38.7 (1.5)	41.8 (1.6)	37.7 (1.7)
Acculturation score[a]	1.7 (0.05)	1.9 (0.05)	1.9 (0.05)
BMI (kg/m^2), %			
BMI<25	15.4 (1.0)	17.4 (1.1)	19.3 (1.3)
25≤BMI<30	38.5 (1.5)	42.0 (1.4)	42.0 (1.5)
BMI≥30	46.1 (1.5)	40.6 (1.4)	38.7 (1.6)
Smoking status, %			
Never smoker	57.2 (1.6)	54.9 (1.5)	52.9 (1.8)
Former smoker	25.6 (1.3)	26.4 (1.5)	25.4 (1.7)
Current smoker	17.2 (1.1)	18.8 (1.2)	21.7 (1.4)
Diabetes, %	35.9 (1.5)	24.7 (1.3)	22.9 (1.4)
Systolic blood pressure, mmHg	130.6 (0.65)	128.4 (0.53)	127.7 (0.51)
Use of anti-hypertensive medications, %	35.3 (1.5)	22.9 (1.3)	20.7 (1.2)
Total cholesterol, mg/dL	207.7 (1.31)	211.8 (1.52)	207.4 (1.31)
HDL-cholesterol, mg/dL	48.7 (0.37)	50.7 (0.40)	50.0 (0.47)
ABI	1.07 (0.006)	1.07 (0.005)	1.08 (0.004)
Accelerometer wear time, hours/d	14.7 [13.0-17.4]	15.4 [13.6-18.4]	16.6 [14.4-19.5]
Sedentary time, hours/d	12.4 [10.7-15.1]	11.7 [9.9-14.5]	10.7 [8.6-13.5]
Light physical activity time, hours/d	2.2 [1.8-2.6]	3.5 [3.2-3.8]	5.2 [4.6-6.0]
Moderate or vigorous physical activity time, mins/d	5.5 [1.4-14.3]	12.0 [5.0-24.0]	20.7 [9.8-37.7]
Total physical activity level, counts/min/d	75.2 [53.9-103.1]	123.6 [94.8-163.4]	193.5 [148.5-261.4]

Values for continuous variables are given as mean (SE) or median [IQI]; values for categorical variables are given as percentage (SE).
Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HDL, high-density lipoprotein; IQI, interquartile intervals; SE, standard error.

Web Table 2. Baseline Characteristics by Tertiles of Moderate/Vigorous Physical Activity, Weighted

	Moderate/Vigorous Physical Activity Time		
Characteristic	**Tertile 1 (Least Active)**	**Tertile 2**	**Tertile 3 (Most Active)**
Total participants, No. (unweighted)	2447	2454	2429
Age, y	59.4 (0.29)	55.6 (0.28)	54.6 (0.23)
Male, %	32.5 (1.3)	45.7 (1.5)	59.0 (1.5)
Hispanic/Latino background, %			
Mexican	29.1 (2.3)	35.4 (2.1)	34.4 (2.0)
Puerto-Rican	15.6 (1.3)	16.2 (1.3)	22.5 (1.6)
Cuban	37.5 (2.7)	23.7 (2.3)	15.3 (1.7)
Others/mixed	17.8 (1.1)	24.7 (1.6)	27.9 (1.6)
Education status, %			
Less than high school	42.1 (1.6)	37.3 (1.6)	40.1 (1.7)
High school or equivalent	19.2 (1.3)	22.1 (1.2)	20.8 (1.1)
Greater than high school	38.6 (1.5)	40.6 (1.7)	39.1 (1.6)
Acculturation score[a]	1.7 (0.06)	1.8 (0.06)	2.0 (0.04)
BMI (kg/m^2), %			
BMI<25	14.0 (1.0)	15.5 (1.0)	22.5 (1.3)
25≤BMI<30	35.6 (1.4)	43.2 (1.5)	44.1 (1.6)
BMI≥30	50.3 (1.5)	41.2 (1.4)	33.5 (1.5)
Smoking status, %			
Never smoker	53.7 (1.6)	56.0 (1.6)	55.9 (1.4)
Former smoker	27.3 (1.3)	25.3 (1.5)	24.6 (1.2)
Current smoker	19.0 (1.2)	18.7 (1.2)	19.6 (1.3)
Diabetes, %	36.3 (1.5)	26.3 (1.2)	21.2 (1.2)
Systolic blood pressure, mmHg	131.2 (0.59)	127.7 (0.52)	127.9 (0.53)
Use of anti-hypertensive medications, %	33.3 (1.5)	27.4 (1.2)	19.1 (1.0)
Total cholesterol, mg/dL	211.2 (1.24)	210.2 (1.26)	205.0 (1.36)
HDL-cholesterol, mg/dL	49.3 (0.39)	49.6 (0.40)	50.4 (0.38)
ABI	1.05 (0.006)	1.07 (0.004)	1.09 (0.004)
Accelerometer wear time, hours/d	14.7 [13.2-17.4]	15.5 [13.7-18.3]	16.7 [14.2-19.5]
Sedentary time, hours/d	11.9 [10.2-14.5]	11.7 [9.9-14.4]	11.7 [9.4-14.1]
Light physical activity time, hours/d	2.8 [2.0-3.6]	3.6 [2.7-4.6]	4.2 [3.2-5.4]
Moderate or vigorous physical activity time, mins/d	2.3 [0.8-4.3]	12.0 [8.8-15.7]	34.7 [26.2-49.6]
Total physical activity level, counts/min/d	74.3 [53.9-100.0]	122.1 [95.8-155.1]	214.7 [166.8-288.4]

Values for continuous variables are given as mean (SE) or median [IQI]; values for categorical variables are given as percentage (SE). Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HDL, high-density lipoprotein; IQI, interquartile intervals; SE, standard error.

Web Table 3. Baseline Characteristics by Tertiles of Total Physical Activity Level, Weighted

	Total Physical Activity Level		
Characteristic	**Tertile 1 (Least Active)**	**Tertile 2**	**Tertile 3 (Most Active)**
Total participants, No. (unweighted)	2444	2443	2443
Age, y	59.8 (0.28)	56.0 (0.26)	53.9 (0.24)
Male, %	34.9 (1.3)	41.7 (1.5)	59.9 (1.6)
Hispanic/Latino background, %			
Mexican	25.3 (2.1)	33.0 (2.1)	40.7 (2.1)
Puerto-Rican	19.4 (1.4)	16.1 (1.2)	18.3 (1.6)
Cuban	32.2 (2.5)	26.4 (2.5)	18.8 (1.9)
Others/mixed	23.0 (1.4)	24.5 (1.5)	22.2 (1.4)
Education status, %			
Less than high school	43.1 (1.6)	39.1 (1.6)	37.4 (1.7)
High school or equivalent	20.1 (1.2)	20.4 (1.3)	21.5 (1.2)
Greater than high school	36.8 (1.5)	40.5 (1.5)	41.1 (1.8)
Acculturation score[a]	1.7 (0.05)	1.8 (0.05)	2.0 (0.06)
BMI (kg/m^2), %			
BMI<25	13.5 (0.9)	17.7 (1.1)	21.0 (1.3)
25≤BMI<30	36.8 (1.5)	42.3 (1.4)	43.5 (1.5)
BMI≥30	49.8 (1.5)	40.0 (1.3)	35.6 (1.5)
Smoking status, %			
Never smoker	56.0 (1.6)	55.9 (1.6)	53.4 (1.6)
Former smoker	26.4 (1.3)	25.1 (1.4)	25.8 (1.3)
Current smoker	17.6 (1.2)	19.0 (1.1)	20.8 (1.4)
Diabetes, %	38.2 (1.5)	25.1 (1.3)	20.6 (1.2)
Systolic blood pressure, mmHg	131.6 (0.60)	128.0 (0.56)	127.2 (0.53)
Use of anti-hypertensive medications, %	36.2 (1.5)	24.6 (1.3)	18.8 (1.1)
Total cholesterol, mg/dL	208.5 (1.20)	212.3 (1.36)	205.9 (1.35)
HDL-cholesterol, mg/dL	49.3 (0.39)	49.9 (0.39)	50.1 (0.45)
ABI	1.06 (0.006)	1.07 (0.004)	1.09 (0.004)
Accelerometer wear time, hours/d	16.0 [13.7-18.6]	15.4 [13.6-18.3]	15.3 [13.6-18.6]
Sedentary time, hours/d	13.5 [11.4-15.8]	11.6 [10.0-14.1]	10.0 [8.4-12.5]
Light physical activity time, hours/d	2.4 [1.9-3.0]	3.6 [3.0-4.4]	4.8 [3.8-5.8]
Moderate or vigorous physical activity time, mins/d	3.0 [1.0-6.8]	12.0 [6.5-19.2]	33.0 [20.8-49.5]
Total physical activity level, counts/min/d	70.4 [53.5-83.2]	126.1 [110.6-143.5]	223.1 [187.5-288.6]
Values for continuous variables are given as mean (SE) or median [IQI]; values for categorical variables are given as percentage (SE). Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HDL, high-density lipoprotein; IQI, interquartile intervals; SE, standard error.			

Web Table 4. Pearson Correlation Between Ankle Brachial Index and Physical Activity Variables

Physical Activity Variables	Ankle Brachial Index
Sedentary time	r=0.03
Light Physical Activity time	r=0.04
Moderate/vigorous physical activity time	r=0.06
Total physical activity level	r=0.05

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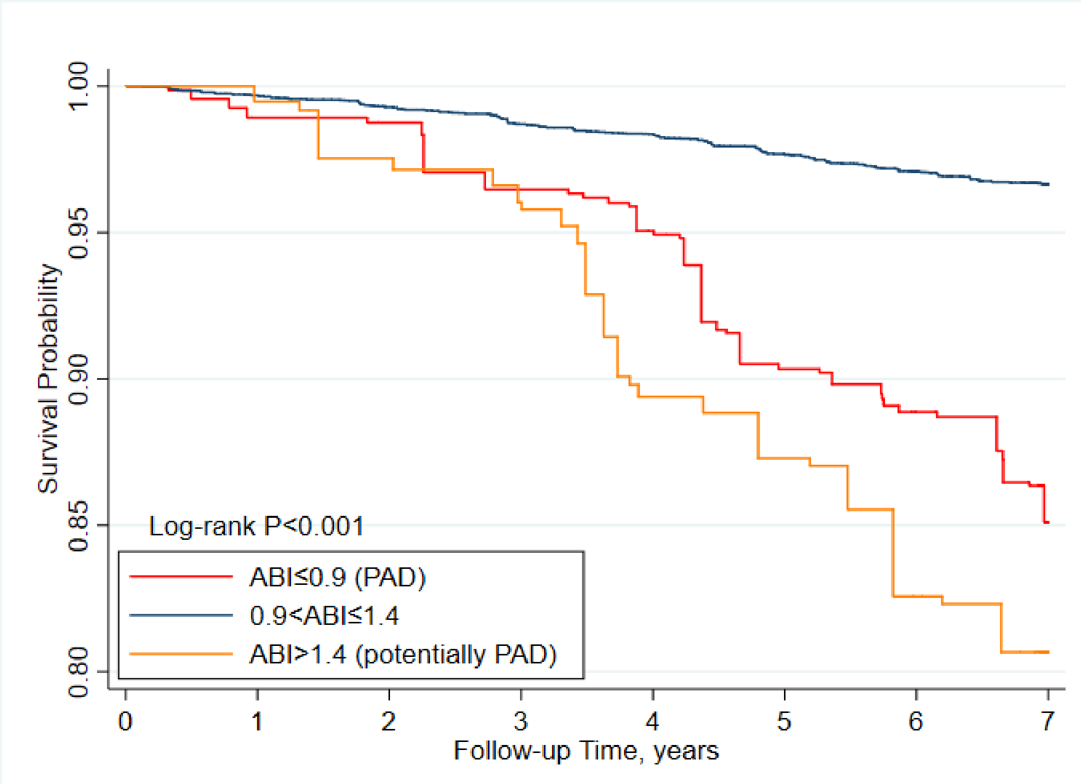
Figure 1. Kaplan-Meier Estimates of Mortality by ABI Categories, Weighted for Sampling Design



Abbreviations: ABI, ankle-brachial index; PAD, peripheral artery disease.

Figure 2. Kaplan-Meier Estimates of Mortality by Tertiles of Physical Activity Variables, Weighted

Figure 2A. Sedentary Time

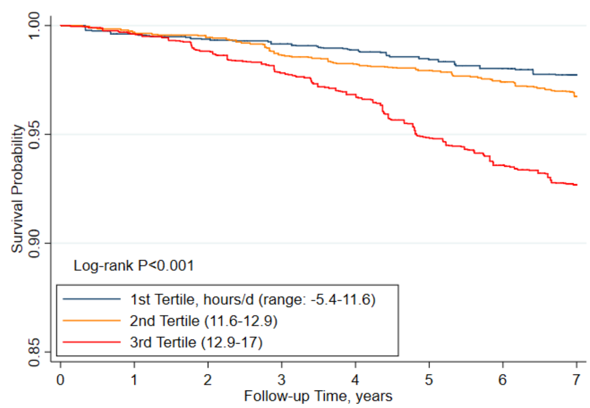


Figure 2B. Light Physical Activity Time

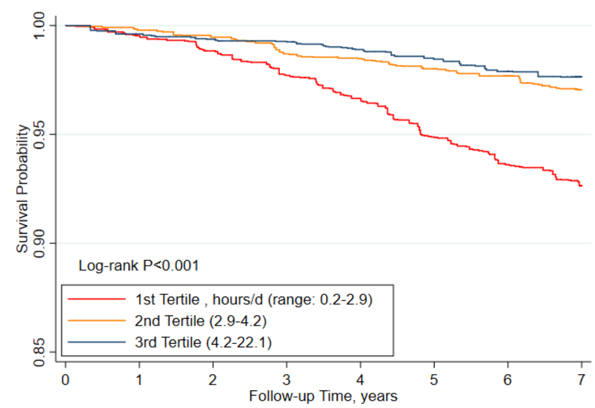


Figure 2C. Moderate/Vigorous Physical Activity Time

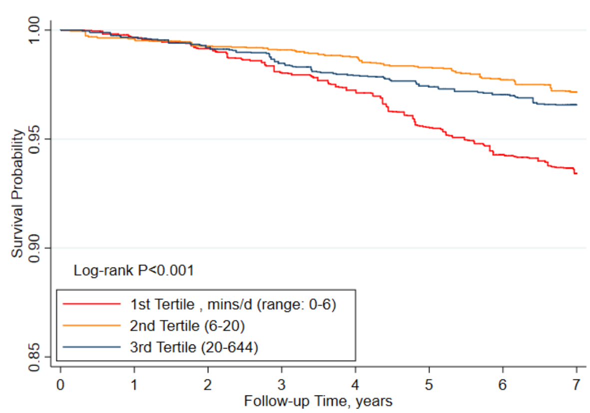
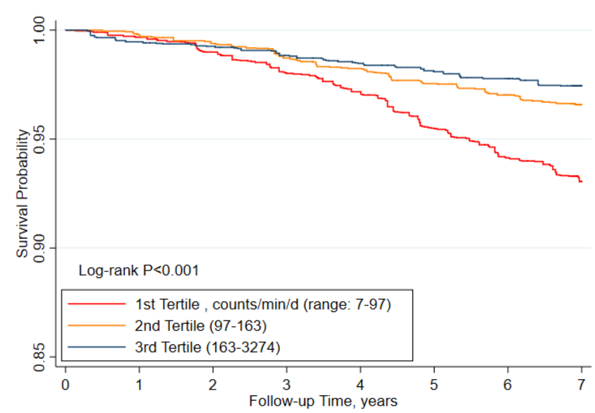


Figure 2D. Total Physical Activity Level



Abbreviations: ABI, ankle-brachial index; PAD, peripheral artery disease.

Figure 3. Survival Estimates of Mortality by Cross-Categories of ABI and Physical Activity, Weighted

Figure 3A. Sedentary Time

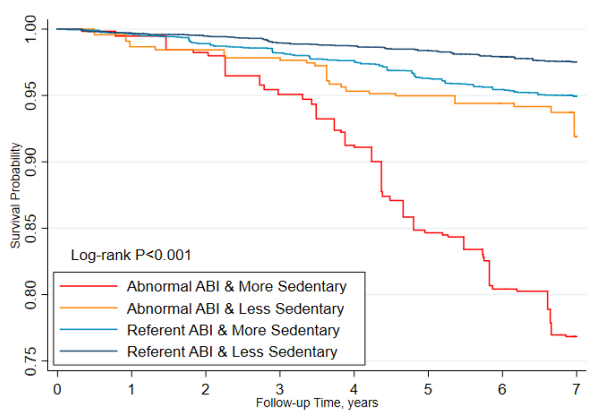


Figure 3B. Light Physical Activity Time

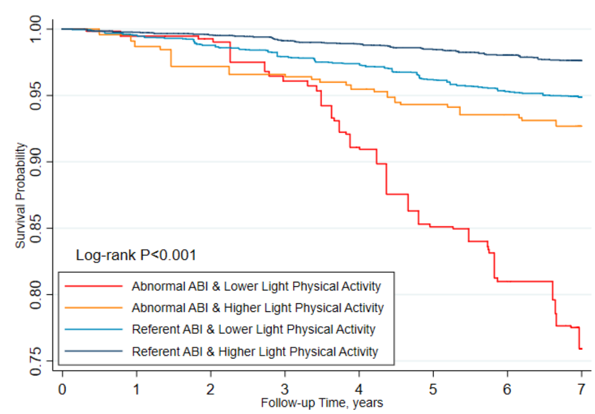


Figure 3C. Moderate/Vigorous Physical Activity Time

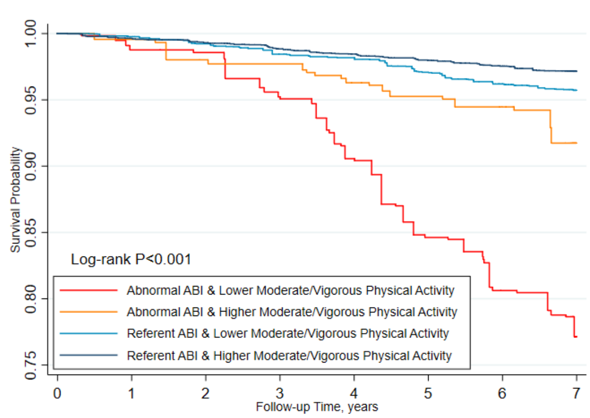
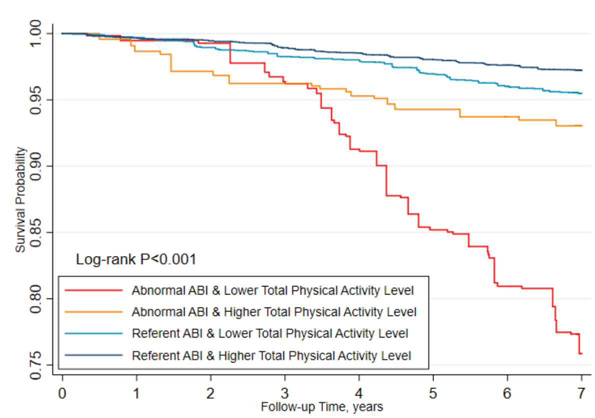
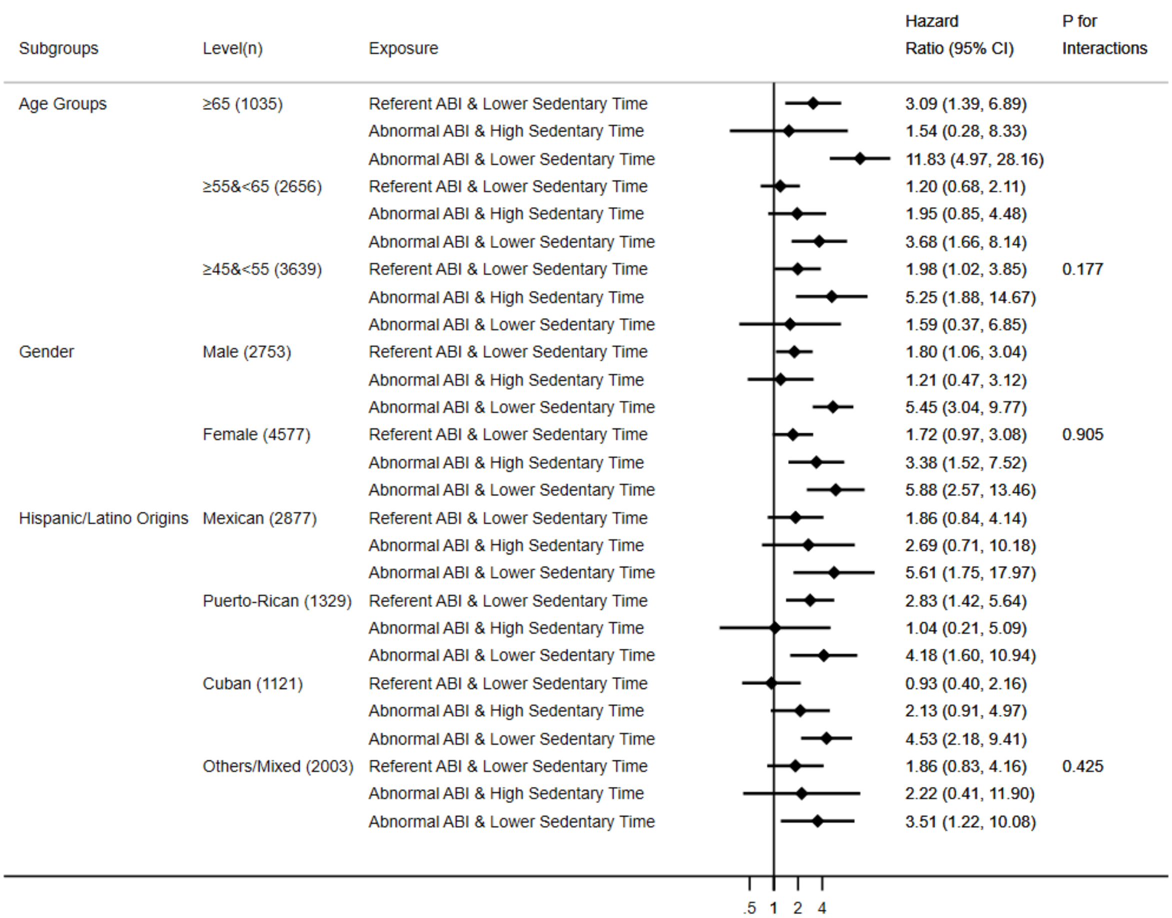


Figure 3D. Total Physical Activity Level



Abbreviations: ABI, ankle-brachial index

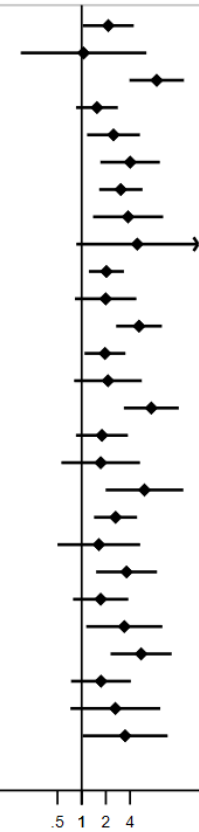
Web Figure 1. Adjusted Hazard Ratios (95%CI) of Mortality by Cross-Categories of ABI and Sedentary Time across Demographic Subgroups



Abbreviations: ABI, ankle-brachial index; CI, confidence interval.

The reference group was defined as individuals with referent ABI and less sedentary. Referent ABI was defined as >0.9 & ≤1.4 and abnormal ABI was defined as ≤0.9 or >1.4. Less sedentary included 1st and 2nd tertiles of sedentary time, whereas more sedentary included 3rd tertile. Hazard ratios were adjusted for age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use.

Web Figure 2. Adjusted Hazard Ratios (95%CI) of Mortality by Cross-Categories of ABI and Light Physical Activity Time across Demographic Subgroups



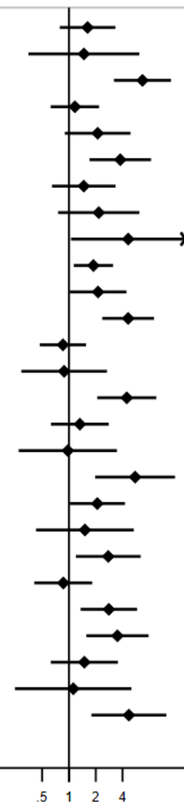
Subgroups	Level(n)	Exposure	Hazard Ratio (95% CI)	P for Interactions
Age Groups	≥65 (1035)	Referent ABI & Lower Light Physical Activity	2.14 (1.03, 4.45)	
		Abnormal ABI & Higher Light Physical Activity	1.06 (0.17, 6.40)	
		Abnormal ABI & Lower Light Physical Activity	8.59 (3.94, 18.75)	
	≥55&<65 (2656)	Referent ABI & Lower Light Physical Activity	1.55 (0.85, 2.82)	
		Abnormal ABI & Higher Light Physical Activity	2.49 (1.17, 5.31)	
		Abnormal ABI & Lower Light Physical Activity	4.01 (1.71, 9.42)	
	≥45&<55 (3639)	Referent ABI & Lower Light Physical Activity	3.07 (1.65, 5.72)	0.253
		Abnormal ABI & Higher Light Physical Activity	3.79 (1.39, 10.34)	
		Abnormal ABI & Lower Light Physical Activity	4.92 (0.86, 28.25)	
Gender	Male (2753)	Referent ABI & Lower Light Physical Activity	2.03 (1.23, 3.36)	
		Abnormal ABI & Higher Light Physical Activity	1.99 (0.82, 4.80)	
		Abnormal ABI & Lower Light Physical Activity	5.18 (2.69, 9.97)	
	Female (4577)	Referent ABI & Lower Light Physical Activity	1.95 (1.09, 3.51)	0.931
		Abnormal ABI & Higher Light Physical Activity	2.12 (0.80, 5.60)	
		Abnormal ABI & Lower Light Physical Activity	7.37 (3.35, 16.19)	
Hispanic/Latino Origins	Mexican (2877)	Referent ABI & Lower Light Physical Activity	1.79 (0.85, 3.76)	
		Abnormal ABI & Higher Light Physical Activity	1.72 (0.56, 5.33)	
		Abnormal ABI & Lower Light Physical Activity	6.05 (1.99, 18.42)	
	Puerto-Rican (1329)	Referent ABI & Lower Light Physical Activity	2.64 (1.43, 4.90)	
		Abnormal ABI & Higher Light Physical Activity	1.64 (0.50, 5.35)	
		Abnormal ABI & Lower Light Physical Activity	3.63 (1.51, 8.67)	
	Cuban (1121)	Referent ABI & Lower Light Physical Activity	1.72 (0.78, 3.81)	
		Abnormal ABI & Higher Light Physical Activity	3.40 (1.14, 10.12)	
		Abnormal ABI & Lower Light Physical Activity	5.49 (2.29, 13.18)	
	Others/Mixed (2003)	Referent ABI & Lower Light Physical Activity	1.74 (0.74, 4.10)	0.900
		Abnormal ABI & Higher Light Physical Activity	2.63 (0.72, 9.52)	
		Abnormal ABI & Lower Light Physical Activity	3.48 (1.03, 11.76)	

Abbreviations: ABI, ankle-brachial index; CI, confidence interval.

The reference group was defined as individuals with referent ABI and more light physical activity. Referent ABI was defined as >0.9 & ≤1.4 and abnormal ABI was defined as ≤0.9 or >1.4. More light physical activity included 2nd and 3rd tertiles of light physical activity, whereas less light physical activity included 1st tertile. Hazard ratios were adjusted for age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use.

Web Figure 3. Adjusted Hazard Ratios (95%CI) of Mortality by Cross-Categories of ABI and Moderate/Vigorous Physical Activity Time across Demographic Subgroups

Subgroups	Level(n)	Exposure	Hazard Ratio (95% CI)	P for Interactions
Age Groups	≥65 (1035)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.62 (0.79, 3.32)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	1.47 (0.35, 6.18)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	6.70 (3.20, 14.03)	
	≥55&<65 (2656)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.17 (0.62, 2.18)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	2.10 (0.90, 4.91)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	3.78 (1.71, 8.36)	
	≥45&<55 (3639)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.47 (0.64, 3.34)	0.918
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	2.16 (0.76, 6.18)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	4.63 (1.05, 20.34)	
Gender	Male (2753)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.88 (1.13, 3.13)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	2.12 (1.02, 4.43)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	4.62 (2.37, 9.02)	
	Female (4577)	Referent ABI & Higher Moderate/Vigorous Physical Activity	0.86 (0.47, 1.56)	0.685
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	0.88 (0.29, 2.67)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	4.46 (2.08, 9.59)	
Hispanic/Latino Origins	Mexican (2877)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.33 (0.63, 2.80)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	0.97 (0.27, 3.46)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	5.53 (1.97, 15.55)	
	Puerto-Rican (1329)	Referent ABI & Higher Moderate/Vigorous Physical Activity	2.08 (1.02, 4.26)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	1.51 (0.43, 5.36)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	2.76 (1.20, 6.39)	
	Cuban (1121)	Referent ABI & Higher Moderate/Vigorous Physical Activity	0.86 (0.41, 1.83)	
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	2.81 (1.35, 5.83)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	3.51 (1.57, 7.85)	
	Others/Mixed (2003)	Referent ABI & Higher Moderate/Vigorous Physical Activity	1.49 (0.63, 3.55)	0.565
		Abnormal ABI & Higher Moderate/Vigorous Physical Activity	1.12 (0.25, 5.04)	
		Abnormal ABI & Lower Moderate/Vigorous Physical Activity	4.71 (1.79, 12.40)	

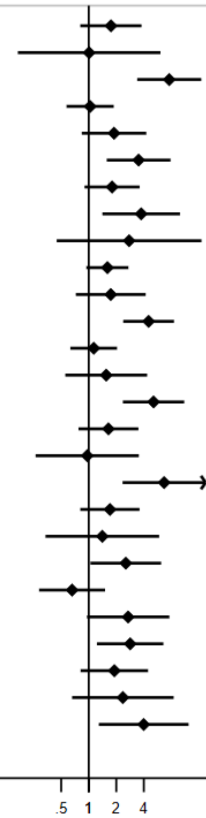


Abbreviations: ABI, ankle-brachial index; CI, confidence interval.

The reference group was defined as individuals with referent ABI and more moderate/vigorous physical activity. Referent ABI was defined as >0.9 & ≤1.4 and abnormal ABI was defined as ≤0.9 or >1.4. More moderate/vigorous physical activity included 2nd and 3rd tertiles of moderate/vigorous physical activity, whereas less moderate/vigorous physical activity included 1st tertile. Hazard ratios were adjusted for age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use.

Web Figure 4. Adjusted Hazard Ratios (95%CI) of Mortality by Cross-Categories of ABI and Total Physical Activity Level across Demographic Subgroups

Subgroups	Level(n)	Exposure	Hazard Ratio (95% CI)	P for Interactions
Age Groups	≥65 (1035)	Referent ABI & Lower Total Physical Activity Level	1.75 (0.81, 3.78)	
		Abnormal ABI & Higher Total Physical Activity Level	1.01 (0.17, 6.08)	
		Abnormal ABI & Lower Total Physical Activity Level	7.58 (3.38, 16.99)	
	≥55<65 (2656)	Referent ABI & Lower Total Physical Activity Level	1.04 (0.57, 1.88)	
		Abnormal ABI & Higher Total Physical Activity Level	1.89 (0.84, 4.25)	
		Abnormal ABI & Lower Total Physical Activity Level	3.51 (1.57, 7.84)	
	≥45<55 (3639)	Referent ABI & Lower Total Physical Activity Level	1.80 (0.90, 3.60)	0.270
		Abnormal ABI & Higher Total Physical Activity Level	3.74 (1.41, 9.95)	
		Abnormal ABI & Lower Total Physical Activity Level	2.76 (0.45, 17.08)	
Gender	Male (2753)	Referent ABI & Lower Total Physical Activity Level	1.60 (0.94, 2.71)	
		Abnormal ABI & Higher Total Physical Activity Level	1.74 (0.72, 4.19)	
		Abnormal ABI & Lower Total Physical Activity Level	4.51 (2.38, 8.55)	
	Female (4577)	Referent ABI & Lower Total Physical Activity Level	1.13 (0.63, 2.04)	0.930
		Abnormal ABI & Higher Total Physical Activity Level	1.55 (0.55, 4.35)	
		Abnormal ABI & Lower Total Physical Activity Level	5.11 (2.36, 11.05)	
Hispanic/Latino Origins	Mexican (2877)	Referent ABI & Lower Total Physical Activity Level	1.64 (0.77, 3.49)	
		Abnormal ABI & Higher Total Physical Activity Level	0.96 (0.26, 3.53)	
		Abnormal ABI & Lower Total Physical Activity Level	6.66 (2.34, 18.96)	
	Puerto-Rican (1329)	Referent ABI & Lower Total Physical Activity Level	1.70 (0.81, 3.59)	
		Abnormal ABI & Higher Total Physical Activity Level	1.41 (0.34, 5.88)	
		Abnormal ABI & Lower Total Physical Activity Level	2.54 (1.04, 6.18)	
	Cuban (1121)	Referent ABI & Lower Total Physical Activity Level	0.66 (0.29, 1.51)	
		Abnormal ABI & Higher Total Physical Activity Level	2.70 (0.96, 7.60)	
		Abnormal ABI & Lower Total Physical Activity Level	2.83 (1.23, 6.55)	
	Others/Mixed (2003)	Referent ABI & Lower Total Physical Activity Level	1.90 (0.82, 4.45)	0.748
		Abnormal ABI & Higher Total Physical Activity Level	2.36 (0.66, 8.48)	
		Abnormal ABI & Lower Total Physical Activity Level	3.99 (1.29, 12.34)	



Abbreviations: ABI, ankle-brachial index; CI, confidence interval.

The reference group was defined as individuals with referent ABI and higher total physical activity level. Referent ABI was defined as >0.9 & ≤1.4 and abnormal ABI was defined as ≤0.9 or >1.4. Higher physical activity level included 2nd and 3rd tertiles of total , whereas lower total physical activity level included 1st tertile. Hazard ratios were adjusted for age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, anti-hypertensive use.

Introduction

Lower-extremity peripheral artery disease (PAD) affects approximately 8.5 million adults in the US[1] and increases the risk of mortality mainly due to cardiovascular disease.[2,3] Thus, the American Heart Association (AHA) and the American College of Cardiology (ACC) 2016 PAD Guideline recommends screening PAD using the ankle brachial index (ABI) among asymptomatic individuals at high risk of PAD (e.g., older adults and middle age adults with PAD risk factors).[4] Moreover, the AHA/ACC 2018 Lipid Guideline recognizes low ABI (≤0.9) as a risk enhancer to guide decision making of lipid lowering therapy.[5]

Reduced physical activity is another important manifestation of PAD and may partially contribute to elevated mortality in PAD.[6-11] However, actually, to our best knowledge, only two small studies (n<500) reported lower physical activity predicting poor prognosis in PAD pateints.[6,7] Moreover, the larger study only investigated PAD patients with intermittent claudication, a small subgroup of PAD, and relied on self-reported physical activity.[6] Compared to self-report, prior studies have shown that objective measurements appeared to capture physical activity more comprehensively and reflect stronger associations with clinical outcomes.[12,13] The other smaller study used accelerometry-based physical activity but could only investigate 225 patients.[7] As a consequence, the AHA/ACC 2016 PAD Guideline describes the potential value of physical activity tracking in PAD patients merely for motivating behavioral changes but not for prognostication.

Also, these two studies only investigated PAD patients and thus were unable to quantify the joint prognostic value of PAD and physical activity. In addition, neither of both studies reported data specific to Hispanics, an ethnic group with high prevalence of two major risk factors of PAD, smoking and diabetes.[14]

To overcome these knowledge gaps, we quantified the independent and joint association of ankle-brachial index (ABI), a first-line diagnostic indicator of PAD, and physical activity, objectively measured via accelerometry, with all-cause mortality over 10 years of follow-up using data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Methods

Study Participants

The HCHS/SOL is a community-based prospective cohort study of 16,415 self-identified Hispanic/Latino adults aged 18-74 years old living in four US communities (Bronx, New York; Chicago, Illinois; Miami, Florida; San Diego, California) at baseline (2008-2011). Details of the cohort design and sampling methods have been published previously.[15,16] Briefly, participants were recruited using a stratified 2-stage probability sampling design.[15] Census block groups were first randomly selected in each of the four communities, and households were randomly selected in each sample block group. The HCHS/SOL included participants with Cuban, Dominican, Mexican, Puerto Rican, Central American, and South American origins.

At baseline, 9,705 participants aged 45-74 were eligible for the assessment of ABI. Of these, we excluded participants with missing ABI values (n=65), non-adherent to wearing accelerometers (n=1,746), missing covariates of interest (n=290), and missing both mortality and hospitalization data (n=166), leaving the final sample size of 7,330 for the current analysis. The study was approved by the institutional review board of each participating institution; all study participants provided written informed consent.

Assessment of ABI

After at least 5 minutes of rest, systolic blood pressures of bilateral brachial, posterior tibial, and dorsalis pedis arteries were measured in supine position using appropriate cuff sizes and a hand-held Doppler probe (Nicolet Elite 100R; Nicolet Biomedical Inc, Golden, CO). The ABI in each leg was calculated using the higher of the posterior tibial or dorsalis pedis blood pressure in each leg divided by the higher of left or right brachial pressure. In general, the lower ABI was used in analyses. When the higher ABI was greater than 1.4 and lower ABI was between 0.9 and 1.4, we used the higher ABI value for the analysis since high ABI is often indicative of arterial non-compressibility and can be prognostic.[3]

Assessment of Physical Activity

At the baseline clinic examination, all participants were asked to wear an omnidirectional accelerometer (Actical, model 198-0200-03; Respironics Co. Inc., Bend, OR) on the iliac crest for 7 consecutive days, except when swimming, bathing, and sleeping. The accelerometer was programed to capture accelerations in counts in 1-minute epoch at a sampling rate of 32 Hz. Previously validated counts/min thresholds were used to classify physical activity intensity levels: sedentary, <100 counts/min; light, 100–1,534 counts/min; moderate, 1,535–3,961 counts/min; and vigorous, ≥3,962 counts/min.[17,18] Nonwear time was defined as at least 90 minutes of zero counts, allowing for 1 or 2 mins of nonzero counts if no counts were detected in a 30-minute upstream window and a 90-minute downstream window, using the Choi algorithm.[19] Adherence to wearing accelerometers was defined as at least 10 hours per day for 3 days or more.

To assess physical activity volume, we calculated total physical activity level (counts/min/d) by dividing total accelerometry counts by wear time in minutes in each day and taking average across the adherent days. For intensity, we used variables that accounted for duration of physical activities in sedentary, light, and moderate or vigorous levels. Sedentary time (hours/d) was determined by summing the daily wear time within the specified acceleration count range (<100 counts/min) and then averaging across all adherent days. To investigate the association of sedentary time independent of wear time when they were highly correlated (r=0.80), we standardized sedentary time by calculating the residuals from the regression of wear time on sedentary time, then adding the expected mean sedentary time of the study population.[20,21] After standardization, sedentary time was no longer correlated to wear time (r<0.001). Average light and moderate/vigorous physical activity time in mins/d were also calculated, which were not strongly correlated with wear time (r<0.06).

Covariates

Age, gender, Hispanic/Latino background (Mexican, Puerto-Rican, Cuban, or others/mixed), education (less than high school, high school or equivalent, greater than high school), acculturation, smoking status (never, former, or current), medical history, and use of medications (e.g., anti-hypertensive and anti-diabetic) were based on self-report. As done previously in a multi-ethnic cohort,[22] the acculturation score was derived by summing a sociocultural subscore based on the language spoken at home and a subscore indicating nativity and years of residence in the US, which ranges from 0 (lowest) to 5 (highest). Body mass index (BMI) was calculated using weight in kilograms divided by height in meters squared (kg/m^2). Sitting blood pressure was calculated by averaging the second and third readings using an automatic sphygmomanometer. Total cholesterol was measured in serum using a cholesterol oxidase enzymatic technique, and high-density lipoprotein (HDL) cholesterol was measured by a direct magnesium/dextran sulfate method (Roche Diagnostics, Indianapolis, IN).[23] Glucose was measured in ethylenediaminetetraacetic acid (EDTA) plasma using a hexokinase enzymatic method (Roche Diagnostics, Indianapolis, IN) and hemoglobin A1C was measured in EDTA whole blood using a Tosoh G7 Automated HPLC Analyzer (Tosoh Bioscience, Inc, South San Francisco, CA).[23] The history of diabetes was defined by fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, 2-h post oral glucose tolerance test ≥200 mg/dL, hemoglobin A1C ≥6.5% or self-reported use of anti-diabetic medications.

Outcomes

The outcome of interest was all-cause mortality, identified by annual follow up interviews, review of vital statistics lists and obituaries of each state, and periodic linkage to the National Death Index. Participants were followed until December 2018, date of death or loss to follow-up, whichever came first.

Statistical Analysis

All statistical analyses were performed incorporating the survey weights to account for the 2-stage probability sampling design. ABI was grouped into following 3 categories: ABI ≤ 0.9 (indicative of PAD),[24] ABI>0.9 and ≤1.4 (reference), and ABI >1.4 (indicative of arterial non-compressibility or potential PAD).[25] The category of ABI>0.9 and ≤1.4 was used as reference.[26,27] Physical activity measurements were also categorized into three groups according to tertiles. The empirically healthiest category of each physical activity was used as reference (i.e., the lowest tertile for sedentary time and the highest tertile for physical activity). Baseline characteristics were summarized by ABI categories and tertiles of sedentary time as mean (standard error, SE) or median [interquartile interval, IQI] for continuous variables and percentage (SE) for categorical variables. We also explored baseline characteristics across tertiles of the other physical activity measures.

For survival analysis, we first estimated survival by categories of ABI and each physical activity variable (sedentary time, light physical activity time, moderate/vigorous physical activity time, and total physical activity level) using the Kaplan-Meier method. Then, we used Cox proportional hazards models to examine the independent associations of ABI and each physical activity variable with all-cause mortality. We adjusted for the following potential confounders: age, gender, Hispanic/Latino background, education, acculturation score, smoking status, BMI, total and HDL cholesterols, diabetes, systolic blood pressure, and anti-hypertensive use. For analysis of ABI, we further adjusted for standardized sedentary time and total physical activity level. For analysis of each physical activity variable, we adjusted for ABI as well as wear time (except for sedentary time already standardized for wear time as noted above).

In addition, to assess joint association of ABI and physical activity, we ran Cox models with cross-categories of ABI and each physical activity variable. To obtain reliable estimates in this analysis, instead of modeling nine cross-categories, we created four categories based on two categories of ABI (merging ≤0.9 and >1.4 as abnormal ABI vs. >0.9 & ≤1.4 [reference][27]) and two categories of physical activity (merging two tertiles vs. the remaining tertile) according to their associations with mortality, as shown subsequently. Statistical interaction between ABI and physical activity was evaluated with the likelihood ratio test.

We conducted sensitivity analyses to evaluate the robustness of our findings. We repeated our analyses in demographic subgroups of age (≥45&<55 vs. ≥55&<65 vs. ≥65 years), gender (male vs. female), and Hispanic/Latino background (Mexican vs. Puerto-Rican vs. Cuban vs. Others). Again, interactions were tested by the likelihood ratio test. All analyses were performed using Stata, version 15.1 (StataCorp, College Station, TX), and a P-value <0.05 was considered statistically significant.

Results

Baseline characteristics

In 7,330 participants at baseline, the mean age was 56.7 years old and 45.2% were men. Of their Hispanic/Latino background, 32.8% were Mexican, 18.0% were Puerto-Rican, 26.0% were Cuban, and the remaining 23.2% reported Dominican, Central or South American, or other/mixed origins. The average ABI was 1.07 (0.003 [standard error, SE]); 5.2% (n=345) and 2.8% (n=162) had ABI ≤0.9 and >1.4, respectively. The average accelerometer wear time was 15.8 (0.08) hours/d (median 15.5 [IQI 13.6-18.5] hours/d). The average total physical activity level was 152.8 (2.41) counts/min/d (median 126.1 [IQI 83.1-187.5] counts/min/d). In terms of physical activity intensity, the average sedentary time was 11.9 (0.07) hours/d (median 11.8 [IQI 9.83-14.4] hours/d) and the participants on average spent 3.6 (0.03) hours/d (median 3.5 [IQI 2.6-4.6] hours/d) in light physical activity and 19.6 (0.55) mins/d (median 11.8 [IQI 4.3-26.0] mins/d) in moderate or vigorous physical activity.

As compared with the referent ABI (>0.9 & ≤1.4), individuals with low (≤0.9) or high ABI (>1.4) were likely to be older, diabetic, and have higher blood pressure, and engage less in physical activity (**Table 1**). The prevalence of current smoking was highest in low ABI, followed by referent ABI and high ABI. When we compared baseline characteristics across tertiles of sedentary time, longer sedentary time was associated with higher risk factor profile (e.g., older age, higher BMI, higher blood pressure, and higher prevalence of diabetes). However, the prevalence of current smoking was lowest in the top tertile of sedentary time. Similarly, a higher risk factor profile was observed with lower activity across the other physical activity measures (Web Table 1-3). ABI values were weakly correlated to each physical activity variable ($|r|<0.06$) (Web Table 4).

Independent associations of ABI and physical activity with mortality

During a median follow up of 7.1 years of follow-up (IQI, 7.0-7.3 and maximum 10.1 years), 314 participants died (5.4% of the weighted study population). When we compared survival among ABI categories, ABI≤0.9 and ABI>1.4 showed a similar pattern up to ~3 years but then ABI>1.4 demonstrated worse prognosis than ABI≤0.9 (7-year survival 79.3% and 83.9%, respectively) (**Figure 1**). The referent ABI had the best prognosis, with 7-year survival of 95.9%. For physical activity, all measures largely demonstrated similar patterns (**Figure 2A-2D**), with the poorest prognosis (7-year survival 91-93%) in the least active group (i.e., the highest tertile of sedentary time and the lowest tertile of the other activity measures) and largely similar survival (7-year survival 95-97%) in the remaining two groups.

After adjusting for each other, potential confounders, and wear time, the associations of ABI and physical activity measures with mortality remained largely consistent (**Table 2**). For ABI categories, the highest hazard ratio (HR) was seen in ABI >1.4 (3.39 [95% CI, 1.84-6.25]), followed by ≤0.9 (2.36 [1.46-3.81]). For physical activity variables, in general, there was a dose-response relationship, but the significant association with mortality was restricted to the least active tertile (e.g., HR=2.50 [1.54-4.07] for 3rd vs. 1st tertile of sedentary time and 2.67 [1.66-4.29] for 1st vs. 3rd tertile of light physical activity). The risk gradient was least evident for moderate/vigorous activity.

Joint association of ABI and physical activity with mortality

When we explored cross-categories of ABI and physical activity measures, abnormal ABI plus the highest sedentary time had an adjusted HR of 5.40 (95% CI 3.31-8.79) and abnormal ABI plus the lowest light physical activity had a similar HR of 5.87 (95% CI 3.53-9.77), when compared to referent ABI plus the more physically active category (i.e., 1st and 2nd tertiles of sedentary time and 2nd and 3rd tertiles of light physical activity) (**Table 3**). The categories with only abnormal ABI or the highest sedentary time or the lowest light physical activity all showed HRs ~2. Generally, similar results were seen for cross-categories of ABI and other two variables (i.e., moderate/vigorous physical activity and total physical activity level), although the adjusted HRs tended to be smaller than those for cross-categories of ABI and sedentary time/light physical activity. No statistically significant interactions between ABI and physical activity measures were found (P-for-interactions >0.1).

The joint associations of abnormal ABI and lower physical activity with mortality were largely consistent in demographic subgroups by age, gender, and Hispanic/Latino background (**Web Figures 1-4**). In almost all comparisons, the highest mortality was observed in abnormal ABI and the least active group. We did not observe any statistically significant interactions in these analyses.

The survival across the four groups by abnormal ABI and physical activity measures is displayed (**Figure 3**). For example, when we looked at sedentary time, the 7-y survival was worst in abnormal ABI plus the least active tertile (74.9%), followed by abnormal ABI alone (91.6%) and the least active tertile alone (93.8%), whereas the best survival was seen in referent ABI plus the remaining more active tertiles (97.0%).

Discussion

To our knowledge, this is the first study evaluating the independent and joint associations of ABI and objectively measured physical activity with all-cause mortality. We also uniquely explored Hispanic/Latino adults, with a few traits (e.g., smoking and diabetes) prone to developing PAD and reducing physical activity. Our study demonstrated that abnormal ABI (≤0.9 or >1.4) and lower physical activity are associated with mortality independently of each other and other potential confounders. As a consequence, individual with both abnormal ABI and lowest physical activity level conferred ~5 times higher mortality risk compared to those without either of these conditions. The joint associations largely remained consistent across age groups, gender, and Hispanic/Latino background. When we contrasted different physical activity measures, they overall demonstrated similar patterns (the least active tertile having elevated mortality risk and the remaining tertile showing similar survival), but the risk gradient appeared most evident for sedentary time and light activity.

The observed U-shaped association of ABI with mortality is generally consistent with previous studies[3,27,28] and likely reflects low ABI as an indicator of PAD and high ABI representing non-compressible arteries. Some studies have reported high prevalence of PAD (~85%) in individuals with ABI>1.4.[29] Of note, high ABI had even slightly worse prognosis than low ABI in our study, which highlights the importance of recognizing high ABI as high risk status. For example, the

AHA/ACC 2016 PAD Guideline recommends using toe-brachial-index (TBI) to diagnose PAD among persons with ABI >1.4.[4] Conversely, the AHA/ACC 2018 Lipid Guideline acknowledges low ABI, but not high ABI, as a risk enhancer of cardiovascular risk. Whether high ABI is particularly prognostic in Hispanics or not would require further investigation.

Regarding physical activity, regardless of activity types, the lowest tertile of physical activity was associated with elevated mortality risk, whereas the remaining two tertiles showed similar prognosis. Moreover, among all physical activity measures, sedentary time and light physical activity appeared to exhibit most evident risk gradient for mortality. These observations seem to have important implications in the context of the current Physical Activity Guidelines for Americans emphasizing the value of moderate- and vigorous-intensity physical activity for health.[30] Our results suggest that actually light physical activity, even at minimal level reducing sedentary time, is associated with improved prognosis. This seems encouraging for many adults, who may not be able to spend 75-150 minutes of moderate- and rigorous-activity a week. Of note, the most active tertile in our study population did not reach the guideline-recommended daily level of 30 minutes of moderate/vigorous physical activity, which might have limited our ability of detecting stronger associations.

Probably the most novel finding of our study is the synergistic contribution of abnormal ABI and low physical activity to mortality. Specifically, individuals with both of these conditions had 5-6 times increased mortality compared to those without either. This finding highlights the potential value of simultaneously and objectively evaluating ABI and physical activity. As we acknowledged above, some clinical guidelines already recommend the measurement of ABI in individuals at high risk of PAD.[4] On the other hand, to our knowledge, the clinical utility of accelerometry-based physical activity has not been established yet. In this context, our results suggest that patients with PAD may benefit from the objective measurement of physical activity. Of importance, the AHA/ACC 2016 PAD Guideline already acknowledges the value of physical activity assessment for behavioral changes in the context of exercise therapy and thus the data should be available in some patients.[4] So, given the greater precision of objectively measured over self-reported physical activity data, it seems worth discussing whether accelerometry-based physical activity evaluation should be utilized for risk classification in this high-risk clinical populations.

Several limitations of this study should also be acknowledged. First, confirmatory imaging data of leg vasculature were not collected in the cohort, thus PAD was only defined using ABI values. Second, although the follow-up time was not short, a relatively small number of deaths could limit the statistical power to detect a significant interaction between ABI and physical activity. Finally, we were unable to assess cause-specific mortality.

In summary, abnormal ABI (≤0.9 and >1.4) and lower objectively measured physical activity were independently and jointly associated with increased mortality risk even after controlling for potential confounders. Our results suggest the importance of objectively evaluating leg vascular health and physical activity. Although the clinical utility of accelerometry-based physical activity measurement is yet to be established, this measurement may be especially valuable for patients with PAD.

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 2020;141:e139-e596.

2. Sigvant B, Lundin F, Wahlberg E. The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. Eur J Vasc Endovasc Surg 2016;51:395-403.

3. Ankle Brachial Index C, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208.

4. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e726-e79.

5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018.

6. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. J Vasc Surg 2008;47:117-22.

7. Garg PK, Tian L, Criqui MH, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. Circulation 2006;114:242-8.

8. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015;175:959-67.

9. Wahid A, Manek N, Nichols M, et al. Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2016;5.

10. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil 2008;15:239-46.

11. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet 2017;390:2643-54.

12. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 2010;122:743-52.

13. Matthews CE, Moore SC, George SM, Sampson J, Bowles HR. Improving self-reports of active and sedentary behaviors in large epidemiologic studies. Exerc Sport Sci Rev 2012;40:118-26.

14. Daviglus ML, Talavera GA, Aviles-Santa ML, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. JAMA 2012;308:1775-84.

15. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:642-9.

16. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:629-41.

17. Colley RC, Tremblay MS. Moderate and vigorous physical activity intensity cut-points for the Actical accelerometer. J Sports Sci 2011;29:783-9.

18. Wong SL, Colley R, Connor Gorber S, Tremblay M. Actical accelerometer sedentary activity thresholds for adults. J Phys Act Health 2011;8:587-91.

19. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc 2011;43:357-64.

20. Moon JY, Wang T, Sofer T, et al. Objectively Measured Physical Activity, Sedentary Behavior, and Genetic Predisposition to Obesity in U.S. Hispanics/Latinos: Results From the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Diabetes 2017;66:3001-12.

21. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17-27.

22. Diez Roux AV, Detrano R, Jackson S, et al. Acculturation and socioeconomic position as predictors of coronary calcification in a multiethnic sample. Circulation 2005;112:1557-65.

23. The Hispanic Community Health Study. Central Laboratory Procedures2011.

24. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453-61.

25. Suominen V, Rantanen T, Venermo M, Saarinen J, Salenius J. Prevalence and risk factors of PAD among patients with elevated ABI. Eur J Vasc Endovasc Surg 2008;35:709-14.

26. Newman JD, Navas-Acien A, Kuo CC, et al. Peripheral Arterial Disease and Its Association With Arsenic Exposure and Metabolism in the Strong Heart Study. Am J Epidemiol 2016;184:806-17.

27. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004;109:733-9.

28. Velescu A, Clara A, Marti R, et al. Abnormally High Ankle-Brachial Index is Associated with All-cause and Cardiovascular Mortality: The REGICOR Study. Eur J Vasc Endovasc Surg 2017;54:370-7.

29. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J Vasc Surg 2008;48:1197-203.

30. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. JAMA 2018;320:2020-8.

Curriculum Vitae

Yumin Gao

101 N Wolfe St. Apt 539
Baltimore, MD 21231
kmgaoyumin@gmail.com
+1 (765)464-9389

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Education

Johns Hopkins Bloomberg School of Public Health	Master of Science Cardiovascular Epidemiology	Expected May 2020
Purdue University	Bachelor of Science Biomedical Engineering with distinction	June 2017

Professional Experience

Corrie Health, Dr. Seth Martin — Baltimore, MD

Research — 03/2020 – Present

- Tasked to rapidly implement a virtual cardiac rehabilitation program for patients affected by COVID-19 through Corrie Health, a mobile health system that aims to improve care post myocardial infarction

Welch Center for Prevention, Epidemiology, and Clinical Research, Dr. Kunihiro Matsushita — Baltimore, MD

Research — 03/2019 – Present

- Conducted survival analysis (Stata Programming) for an observational study that compares mortality prognosis among four different atherosclerotic groups using probability sampled data (NHANES data)
- Analyzed population-level data (R Programming) and created series of heat maps that highlight global hypertension management and edited patient education videos (Final Cut Pro X) for the Resolve initiative
- Co-hosting a weekly research seminar that introduces emerging technology and service tools for clinical research; conducting literature review for international implementation

projects on sodium reduction

Duke Clinical Research Institute, Dr. Neha Pagidipati/Dr. Eric Peterson — Durham, NC
Clinical Research Intern — 10/2017 – 03/2019

- Drafted and published a narrative review summarizing barriers to providing evidence-based care and opportunities for optimizing clinical management for persons with cardiovascular disease and type-2-diabetes
- Designed, coordinated, and analyzed (REDCap) a qualitative survey study that explored knowledge and perceived barriers to prescribing GLP1RA and SGLT2i among 90 clinicians across 6 Duke clinics
- Interviewed leaders from patient organizations (e.g. NORD, FH Foundation) and drafted a health policy chapter on how patient advocacy organizations had evolved in their roles of catalyzing cardiovascular research

Weldon School of Biomedical Engineering, Dr. Pedro Irazoqui — West Lafayette, IN
Undergraduate Research — 11/2015 – 05/2017

- Manufactured, tested, and developed circuit boards of implantable devices designed to stimulate animal vagal nerves and record responsive electrical signals
- Analyzed compound cytokine level data in mice collected from chronic stressing experiments to evaluate the effectiveness of implantable devices in reducing serum cytokine concentrations
- Constructed a user interface (Xcode/Swift) and software architecture that can recognize patterns in images and videos (Python/PyTorch) for an artificial vision project

Awards, Honors and Membership in Honorary Societies

Nancy Fink Fund for Scholarship and Service – Johns Hopkins Bloomberg School of Public Health	2020
Y-Prize Grand Prize Winner - Penn Engineering, Wharton's Mack Institute for Innovation Management, Penn Wharton Entrepreneurship and the Penn Center for Innovation	2020
Master's Scholarship – Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology	2019
Iron Key – Honor Society that serves the Student Advisory Board for the President of Purdue University (10 senior students per year, by nomination only)	2016-2017

Peer-reviewed Publications

Matsushita K, Ding N, Kou M, Hu X, Chen M, **Gao Y**, Honda Y, Dowdy D, Mok Y, Ishigami J, Appel L J. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. Circulation 2020. (Submitted)

Gao Y, Peterson E, Pagidipati N. Barriers to prescribing glucose-lowering therapies with cardiometabolic benefits. Am Heart J 2020.

Gao Y, Hua S, Mok Y, Qi Q, Chen G, Allison A M, Kaplan R, Matsushita K. Abstract 32: Joint Associations of Peripheral Artery Disease and Objectively-measured Physical Activity With Mortality: The Hispanic Community Health Study / Study of Latinos. Circulation. 2020

Matsushita K, **Gao Y**, Yingying S, et al. Comparative mortality according to peripheral artery disease and coronary heart disease/stroke. Eur. Heart J. 2020. (Submitted)

Gao Y, Peterson E, Pagidipati N. Opportunities for improving use of evidence-based therapy in patients with type 2 diabetes and cardiovascular disease. Clin Cardiol 2019.

Presentations

"Joint associations of peripheral artery disease and objectively-measured physical activity with mortality the Hispanic Community Health Study / Study of Latinos (SOL)"	AHA EPI LIFESTYLE 2020 Scientific Sessions (Physical Activity/Sedentary Time Session), Phoenix, AZ	March 5, 2020
"Joint associations of peripheral artery disease and objectively-measured physical activity with mortality	Welch Center Research in Progress Seminar, Baltimore, MD	February20,2020
"A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation"	Emerging Cardiovascular Epidemiology Research Seminar, Baltimore, MD	April 19, 2019

Extracurricular Experience

Y-Prize Invention Competition, University of Pennsylvania — Philadelphia, PA
Co-founder of Metal Light/ Grand Prize Winner 2020 — 09/2019 – Present

- Created an affordable and easy-to-use LED light that extracts energy from scrap metal surfaces to provide clean light for off-grid communities globally, using technology from an electrochemical lab at U Penn

- Playing a primary role in overseeing product manufacturing in China, marketing research, and partnerships

Food Recovery Network, Purdue University — West Lafayette, IN
Co-founder — 10/2015 – 05/2017

- Co-founded an ongoing campus-wide volunteering program that diverts on average over 1000 pounds of food waste from two university cafeteria locations to a local homeless housing center

Timmy Global Health, Purdue University — West Lafayette, IN/Quito, Ecuador
Medical Brigade Leader/ Media Director — 03/2015 – 05/2017

- Recruited 3 US clinicians and trained 16 student volunteers, and then fundraised/organized a medical brigade that provided free primary care to over 550 patients in five underserved communities in south Quito
- Managed a media team of 4 students and created 2 documentaries and 10+ infographics to raise the awareness of global health disparities